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BLADDER CANCER

Stem cells repopulate tumours

The effectiveness of chemotherapy can be limited by the development of progressive resistance. Newly published research shows that, in bladder tumours, apoptosis caused by chemotherapy can release prostaglandin E_2 (PGE_2), activating quiescent cancer stem cells (CSCs) to repopulate the tumours. Blocking PGE_2 signalling attenuates chemoresistance in mouse models, and could provide a new treatment modality for bladder cancer.

Bladder urothelial carcinomas can contain cells at various stages of differentiation, including poorly differentiated cytokeratin 14-positive ($CK14^+$) CSCs, the presence of which correlates with poor survival. Kurtova *et al.* have now shown that these CSCs persist, and are even enriched, following chemotherapy in patients and in xenografts, despite overall reduction in tumour size.

The $CK14^+$ CSCs are quiescent cells that are only induced to proliferate following chemotherapy. Cytotoxic treatment causes apoptosis in rapidly proliferating cancer cells, and various factors, including PGE_2, are released from apoptotic cells. Experimental simulation of chemotherapy in urothelial carcinoma cells *in vitro* demonstrated elevation of PGE_2 release and cellular expression of the inducible prostaglandin synthase PTGS2 (COX2). Treatment of urothelial carcinoma cells with either an exogenous PGE_2 analogue or PGE_2-containing post-chemotherapy cell-culture supernatant increased levels of sphere-forming CSCs, whereas addition of either a PGE_2-neutralizing antibody or the COX2 inhibitor celecoxib to the supernatant reduced the generation of sphere-forming cells.

The response of the bladder CSCs to PGE_2 resembles the repopulation of normal tissues in wound healing, and gene-expression profiling of chemoresistant bladder tumours and xenografts revealed enrichment of a 'wound-response' gene signature (including *PTGS2*) by chemotherapy. This response was abrogated by combining celecoxib treatment with the chemotherapy. In xenograft models of advanced bladder cancer, one of which was derived from a patient who was resistant to cytotoxic treatment, addition of celecoxib to multiple cycles of gemcitabine–cisplatin chemotherapy inhibited the progressive development of chemoresistance, as evidenced by reductions in tumour volume and expansion of $CK14^+$ CSCs. This effect became more pronounced as the number of treatment cycles increased.

The progressive response of tumours has implications for current prognostic practice and future therapeutic approaches. "Therapeutic response to chemotherapy cannot solely be dependent on the genetics of the initial pretreatment tumours, and therapeutic responses are unlikely to be predicted by gene-expression profiles alone," says Keith Syson Chan, who led the study. The potential to use celecoxib, an FDA-approved drug, could be very important for treatment of bladder cancer, as no approved targeted therapy is currently available. Refinement of celecoxib administration, for instance by limiting it to intervals between chemotherapy cycles, could further improve its effectiveness.

Robert Phillips

Original article Kurtova, A. V. *et al*. Blocking PGE2-induced tumour repopulation abrogates bladder cancer chemoresistance. *Nature* doi:10.1038/nature14034